REMARKS

Status of Claims

Claims 1-11 are pending.

Claims 1-4 have been amended.

Applicants attach Appendix A with the newly revised claims, primarily for the Examiner's convenience.

Rejections under 35 USC § 112 second paragraph

Claims 1-4 have been amended to more clearly define the invention. Specifically, claim 1 has been amended to further clarify the phrase "comprising a central hydrophobic domain" by stating "wherein the central hydrophobic domain comprises at least amino acid residues 22-30 of the native HCV NS4A peptide". Basis for this amendment is found on page 10, lines 1-7; as well as page 3, lines 7-10; and page 7, lines 28-30. Applicants also teach that flanking regions of the central hydrophobic domain include amino acid residues 13-32 of the native HCV NS4A peptide. Support for the flanking regions can be found on page 3, lines 4-7, 10-16, 21-24; page 7, lines 27-34; page 10, lines 2-7 and page 11, lines 3-9.

To further clarity the invention, claim 2 has been amended from "at least about" to "at least"; and claims 3 and 4 have been amended from "consisting essentially of" to "consisting of". No new matter has been added by virtue of these claim amendments. Applicants believe these amendments overcome the Examiner's rejection regarding indefiniteness.

Rejections under 35 USC § 103

Under 35 USC § 103(a) Examiner rejected claims 1-11 as being unpatentable over Kim *et al.* (Cell 87:343-355, October 18, 1996) in view of Dasmahapatra *et al.* (U.S. 5,843,752).

The Examiner noted that Kim *et al.* discloses the three dimensional structure of the HCV NS3 protease domain complexed with a synthethic NS4A cofactor peptide as well as structural features of this complex. In addition, the Examiner alleged that the structure disclosed by Kim *et al.* suggests fusing the C-terminus of the essential portion of the NS4A peptide to the N-terminus of the catalytic domain using an appropriate spacer to abrogate the need for an exogenous cofactor.

Applicants respectfully submit that knowledge of the components that are necessary for an active NS3 protease construct and information on their general

orientation are not sufficient to render the particularly claimed NS4A/NS3 recombinant complexes obvious.

Those skilled in the art know that the engineering, expression and proper folding of Applicants' specific protease complexes would have been anything but obvious when the present invention was made. There is no information in either the Kim *et al.* or the Dasmahapatra *et al.* reference that would suggest the tethering of the NS4A cofactor central hydrophobic region to the N-terminus of the NS3 protease domain -- all prior NS3/NS4A complexes placed the NS4A region at the C-terminus, where it is naturally expressed in the HCV polyprotein. More importantly, there is nothing in the combined disclosure of the cited references that would suggest the claimed complexes would be properly expressed and folded to yield a stable, active protease construct. Considering the information available at the time of the invention about protein folding in general, and about HCV polyprotein processing in particular, such a venture would have raised significant doubts in the mind of one skilled in the art with respect to the likelihood of success.

It is well known that protein folding in biotechnology can be unpredictable. Transcription and translation of recombinant genes do not always lead to the accumulation of a correctly folded, fully active protein. See, e.g., Mechanisms of Protein Folding, R.H. Pain, 1994, Oxford University Press, New York, NY pp. 229-231. The literature is replete with examples of proteins which fail to fold correctly when they are expressed recombinantly in bacteria. Particularly when a protein has multiple subunits, many factors come into play in the proper folding and subunit assembly of a protein. Id. at pp. 160-169. (Copies of both sections are enclosed for the Examiner's convenience). Before Applicant successfully produced the single-chain recombinant complexes of the claimed invention, one would have had no way of knowing whether the re-engineering of the HCV viral domains would have resulted in a stable, active protease construct.

Moreover, what was known about viral processing of the full-length HCV polyprotein would have taught away from the present invention. The skilled artisan was aware that when the HCV viral polyprotein is expressed from the HCV genome, the NS2 protein is cotranslationally cleaved at the NS2-NS3 junction. See, e.g., Pieroni *et al.*, 1997, J. Virology 71(9):6373-6380 (copy enclosed). Thus, cleavage of the protein which is normally expressed at the N-terminus of NS3 occurs before normal folding of the NS3 protease can take place. There is nothing in the reference by Kim *et al.* or Dasmahapatra *et al.* that suggests covalent fusion of a protein to the N-terminus of the NS3 protease would not prevent proper folding of the protease. Furthermore, there is nothing in any of the references that would suggest that fusion of the particular protein that Applicants

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successfully expressed at the NS3 N-terminus – that is, the NS4A cofactor hydrophobic region and a flexible linker – would allow proper expression and folding. Given the multitude of factors that must come together to allow production for a properly folded, active viral protein, it simply cannot be said that the claimed active complexes are obvious.

It is believed that the foregoing arguments and amendments overcome all objections and rejections set forth by the Examiner and that this application is now in condition for allowance. Early and favorable action is therefore solicited.

With regard to the Draftsperson's objection of drawings, Applicants wish to postpone filing of new drawings until receipt of the Notice of Allowability.

Please charge any additional fees or credit overpayment to Deposit Account No. 19-0365.

Respectfully submitted,

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